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Febuxostat is superior to allopurinol in delaying the progression of renal impairment in patients with chronic kidney disease and hyperuricemia

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Abstract

Purpose This study aimed to compare efficacy of renal-protective function between febuxostat and allopurinol in patients with chronic kidney disease (CKD) and hyperuricemia (HUA).

Methods Totally 152 CKD stage 2–3 patients complicated with HUA were recruited. According to their uric acid-lowering therapy, there were 67 patients included in febuxostat group and 85 in allopurinol group, respectively. Estimated glomerular filtration rate (eGFR), serum creatinine (Scr), 24-h proteinuria, serum uric acid (SUA) were measured at M0, M1, M3 and M6 after the treatment. Primary outcome was proportion of patients showing ≥ 10% decline in eGFR from baseline at M6.

Results The eGFR at M6 was numerically higher at M6 and eGFR change (M6–M0) was increased in febuxostat group compared with allopurinol group. Most importantly, the proportion of patients showing a ≥ 10% decline in eGFR from baseline at M6 was reduced in febuxostat group compared with allopurinol group. Multivariate logistic regression analyses further validated that febuxostat vs. allopurinol was an independent predictor for reduced risk of eGFR decline ≥ 10% from baseline. Besides, SUA change (M6–M0) was decreased, but Scr change (M6–M0) and 24-h proteinuria change (M6–M0) were similar in febuxostat group compared with allopurinol group.

Conclusions Febuxostat presents a superior effect in delaying renal impairment progression compared with allopurinol in CKD patients complicated with HUA.

Keywords Febuxostat · Allopurinol · Chronic kidney disease · Hyperuricemia · Uric acid-lowering therapy

Introduction

Chronic kidney disease (CKD), which is defined as the disorder of estimated glomerular filtration rate (eGFR) and the presence of albuminuria, becomes more and more prevalent in recent decades and affects almost 119.5 million people in China [1, 2]. Hyperuricemia (HUA) is a condition characterized by abnormal increase of serum uric acid (SUA), and it is suggested that HUA is not only a common complication of CKD, but also responsible for progression of CKD by inducing endothelial dysfunction, formation of urate crystal deposition and kidney injury [3]. A wealth of clinical data supports the view that HUA is an independent risk predictor for onset as well as progression of CKD [4, 5]. Furthermore, emerging evidences reveal that uric acid-lowering therapy (ULT) targeting SUA effectively delays renal impairment as well as retards kidney disease progression, such as lowering Scr, reducing the incidence of end-stage renal disease, in CKD patients complicated with HUA [6].

Currently xanthine oxidase inhibitors, as one of ULT-related drugs, reduce SUA level by blocking the transformation of hypoxanthine to xanthine and of xanthine to uric acid [7]. Allopurinol is a traditional competitive xanthine oxidase inhibitor and is metabolized to the oxypurinol, which

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has been used as the cornerstone of HUA and gout clinical management since its introduction in 1966 [8]. However, it requires dose adjustment due to its adverse effects as well as toxicity in patients with renal impairment [9]. Febuxostat, structurally differing from allopurinol, is a novel selective xanthine oxidase inhibitor, which is metabolized by the liver and excreted via both urine and feces [10]. Compared with allopurinol, febuxostat can exert an effect of uric acid-lowering without serious adverse events, which has been suggested as a priority for HUA patients with renal impairment [11, 12]. Considering that the higher SUA level is correlated with the promoted progression of CKD, and febuxostat has superior effect of lowering SUA with less renal impairment to some extent, we hypothesize that febuxostat has a stronger renal-protective effect compared with allopurinol in treating CKD patients complicated with HUA. However, related data are limited. Therefore, we designed the present study and compared the renal-protective effect between febuxostat and allopurinol in treating Chinese CKD patients complicated with HUA.

Methods

Patients

From January 2016 to December 2017, 152 CKD patients complicated with HUA who underwent ULT at Wuhan Fifth Hospital were consecutively recruited in this prospective cohort study. The inclusion criteria consisted of: (1) diagnosed as CKD according to the "Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease" [13]; (2) complicated with HUA, which was defined as serum uric acid (SUA) ≥ 7 mg/dL for male, and SUA ≥ 6 mg/dL for female [14]; (3) CKD stage 2–3 (estimated glomerular filtration rate (eGFR) of 30–89 mL/min/1.73 m^2) [15]; (4) age above 18 years; (5) intended to receive the ULT for at least 6 months; (6) able to be regularly followed up. Following patients were excluded: (1) underwent ULT within 3 months by use of febuxostat, allopurinol, benzbromarone, thiazide diuretics or other drugs; (2) concurrent with acute kidney injury, nephrotic syndrome, obstructive nephropathy or other complications that may lead to a rapid decline of renal function (e.g., vasculitis, systemic lupus erythematosus, etc.); (3) undergoing dialysis or had a history of kidney transplantation; (4) suffering from active gout; (5) had unstable angina, congestive heart failure, myocardial infarction, or a history of coronary artery bypass surgery, traumatic recanalization or stroke; (6) had a history of severe infection or malignancies; (7) pregnant or lactating women. The present study was approved by the Ethics Committee of The Fifth Hospital of Wuhan, and all participants signed the informed consents before initiation of study.

Baseline data collection

After enrollment, baseline data were documented including (1) demographic information: age, gender and body mass index (BMI); (2) history of smoking and drinking; (3) chronic complications: hypertension, diabetes mellitus, ischemic heart disease, dyslipidemia, hypothyroidism, asthma and chronic obstructive pulmonary disease (COPD).

Grouping and treatment

After the patients met the inclusion criteria and signed the informed consents before the initiation of study, those patients were enrolled in our study and intended to receive the ULT for at least 6 months. As for which ULT regimen they would use, clinical physician gave patients alternative ULT regimens (febuxostat/allopurinol) according to the clinical status of patients, and stated the description of two drugs (advantage, adverse effect, cost, etc.). And then patients selected the suitable ULT regimen according to personal willingness of themselves and clinical status. 67 patients who selected the febuxostat for ULT were allocated to febuxostat group, and 85 patients who selected allopurinol for ULT were allocated to the allopurinol group. In the febuxostat group, patient was treated with febuxostat for a total of 6 months, and febuxostat was given to patients at an initial dose of 20 mg/day po in the first month, then according to individual status, it was gradually increased to a maximum dose of 40 mg/day po if the level of SUA was above 7 mg/dL for male, and the level of SUA was above 6 mg/dL for female. In the allopurinol group, patients were treated with allopurinol for total 6 months, and allopurinol was given to the patients at an initial dose of 100 mg/day po in the first month, then according to individual status, it was gradually increased to a maximum dose of 200 mg/day po if the level of SUA was above 7 mg/dL for male, and the level of SUA was above 6 mg/dL for female. Patients would withdraw from study if they stopped using the drugs for ULT or switched the drugs for ULT within 6 months after initiation of study for the reasons as followed: (1) due to the poor efficiency of drugs, some patients switched the drugs for ULT. (2) Patients stopped the drugs for ULT by personal decision or adverse events. Besides, other combined drugs that patients used during study (except for ULT) were required to be documented, such as loop diuretics, calcium ion antagonist, angiotensin receptor blocker/angiotensin converting enzyme inhibitors (ARB/ACEI), β-receptor antagonist, and statin drugs.

Measurements

Scr, 24-h proteinuria and SUA of all patients were measured at baseline (M0), first month after initiation of ULT (M1), third month after initiation of ULT (M3), and at the end of study (M6). And the eGFR was calculated at same time point according to the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [16]: $eGFR = 141 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age}$ [1.018 if female] [1.159 if black], where Scr was serum creatinine (in mg/dL), k was 0.7 for females and 0.9 for males, α was 0.329 for females and 0.411 for males, min was the minimum of Scr/k or 1, and max was the maximum of Scr/k or 1. And CKD-EPI equation has been validated in Chinese population [17]. In our study, Scr was measured by creatinine oxidase assay with the biochemical analyzer (Hitachi, 7600-020E, Japan).

Outcome assessment

The primary outcome was the proportion of patients showing a ≥ 10% decline in eGFR from baseline at M6 [18]. The secondary outcomes were (1) the change of eGFR from M0 to M6; (2) the change of Scr from M0 to M6; (3) the change of 24-h proteinuria from M0 to M6; (4) the change of SUA from M0 to M6, and (5) the incidence of cardiovascular mortality and major adverse cardiovascular events (MACE) which was identified as cardiac death, nonfatal myocardial infarction, and revascularization during the 6 months [19].

Statistical analysis

Intention-to-treat (ITT) analysis was performed in this study. Statistical analysis was performed by use of SPSS 24.0 software (IBM, Chicago, IL, USA), graph plotting was carried out using GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, CA, USA). Data were described as mean and standard deviation (SD) or count (percentage). Difference between two groups was determined by the t test or Chi-square test. Variables affecting eGFR decline ≥ 10% from baseline were assessed by univariable and multivariable logistic regression model analyses. All tests were two-sided and $P < 0.05$ indicated a significant difference.

Results

Study flow

In the present study, 284 CKD patients were initially screened, while 132 of them were excluded (including 111 patients who disobeyed the inclusion criteria or met the exclusion criteria, and 21 patients who disagreed to sign informed consents) (Fig. 1). The remaining 152 CKD patients at stage 2–3 complicated with HUA were recruited, with 67 cases in the febuxostat group and 85 cases in the allopurinol group according to the ULT regimen. During 6-month follow-up, there were 6 total withdrawals in febuxostat group (including 1 patient with end-stage renal disease, 2 lost follow-up, 3 patients stopping ULT or switching ULT regimen during study) and 11 total withdrawals in allopurinol group (including 1 patient with end-stage renal disease, 3 lost follow-up, 7 patients stopping ULT or switching ULT regimen during study). Finally, all 67 patients in febuxostat group and all 85 patients in allopurinol group were included in final analysis based on ITT principle. And the analysis based on per protocol (PP) observed the similar trend as the analysis based on ITT principle, which was not exhibited to avoid repetition.

Baseline characteristics

The mean age of patients in febuxostat group and allopurinol group was 62.6 ± 7.0 years and 61.1 ± 9.0 years, respectively (Table 1). There were 50 (74.6%) males and 17 (25.4%) females in febuxostat group; and there were 65 (76.5%) males and 20 (23.5%) females in allopurinol group. Most importantly, no difference in age, gender, BMI, history of smoking, history of drinking, chronic complications, combined medications, SUA, eGFR, CKD stage, Scr and 24-h proteinuria was observed between two groups (all $P > 0.05$). The detailed baseline characteristics are displayed in Table 1.

Comparison of eGFR

There was no difference of eGFR between febuxostat group and allopurinol group at M0 ($P = 0.870$), M1 ($P = 0.663$), M3 ($P = 0.434$), while febuxostat group presented numerically higher eGFR compared with allopurinol group at M6 without statistical significance ($P = 0.053$) (Fig. 2a). The eGFR change (M6–M0) was increased in febuxostat group (4.69 ± 12.92) compared with allopurinol group (− 0.42 ± 9.89) ($P = 0.008$) (Fig. 2b). Most importantly, the proportion of patients showing a ≥ 10% decline in eGFR from baseline was decreased in febuxostat group (17.9%) compared with allopurinol group (34.1%) ($P = 0.025$) (Fig. 2c). These data above indicated that febuxostat had a superior effect on attenuating eGFR decline compared with allopurinol in CKD patients complicated with HUA.

Factors affecting eGFR decline ≥ 10% from baseline

Univariate logistic regression analyses revealed that febuxostat vs. allopurinol (OR 0.421, $P = 0.028$) and SUA (OR 0.755, $P = 0.043$) was negatively correlated with eGFR

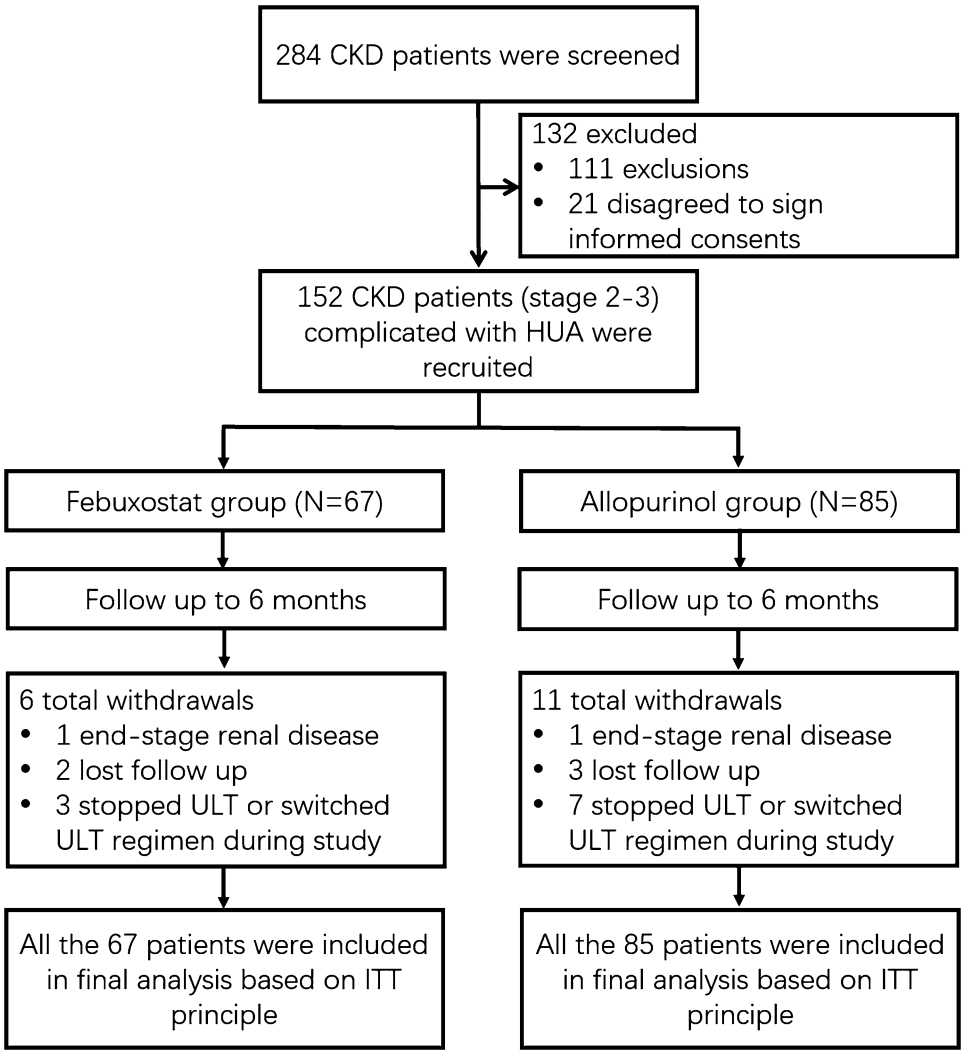

Fig. 1 Study flow. *CKD* chronic kidney disease, *HUA* hyperuricemia, *ULT* uric acid-lowering therapy, *ITT* intention-to-treat

decline ≥ 10% from baseline, while diabetes mellitus (OR 2.710, $P = 0.011$) was positively correlated with eGFR decline ≥ 10% from baseline (Table 2). And multivariate logistic regression analyses further exhibited that febuxostat vs. allopurinol (OR 0.234, $P = 0.017$), BMI (OR 0.717, $P = 0.004$), SUA (OR 0.314, $P < 0.001$) were independent predictors for reduced risk of eGFR decline ≥ 10% from baseline, while diabetes mellitus (OR 17.606, $P < 0.001$), asthma or COPD (OR 12.350, $P = 0.009$) were independent predictors for increased risk of eGFR decline ≥ 10% from baseline.

Comparison of Scr and 24-h proteinuria

Scr was similar at M0 ($P = 0.999$), M1($P = 0.999$) and M3 ($P = 0.223$) but decreased at M6 ($P = 0.016$) in febuxostat group compared with allopurinol group (Fig. 3a). Scr change (M6–M0) was numerically decreased in febuxostat group (− 0.04 ± 0.45) compared with allopurinol group (0.06 ± 0.25), while without statistical significance ($P = 0.085$) (Fig. 3b). The 24-h proteinuria was similar between two groups at M0 ($P = 0.562$), M1 ($P = 0.501$), M3 ($P = 0.450$) and M6 ($P = 0.934$) (Fig. 3c). There was no difference of 24-h proteinuria change (M6–M0) between febuxostat group (− 0.43 ± 0.46) and allopurinol group (− 0.37 ± 0.42) ($P = 0.459$) (Fig. 3d). These data suggested that febuxostat was more potent in reducing Scr to some extent compared with allopurinol in CKD patients complicated with HUA.

Comparison of SUA

There was no difference of SUA between febuxostat group and allopurinol group at M0 ($P = 0.936$), M1 ($P = 0.418$), M3 ($P = 0.498$), while febuxostat group exhibited numerically lower SUA at M6 compared with allopurinol group to some extent ($P = 0.059$) (Fig. 4a). The SUA decline (M6–M0) was greater in febuxostat group (− 3.42 ± 1.36)

Table 1 Characteristics of patients

Items	Febuxostat group ($N=67$)	Allopurinol group ($N=85$)	P value
Age (years), M ± SD	62.6 ± 7.0	61.1 ± 9.0	0.243
Gender, no. (%)			0.793
Male	50 (74.6)	65 (76.5)	
Female	17 (25.4)	20 (23.5)	
BMI (kg/m^2), M ± SD	24.1 ± 2.9	23.9 ± 2.8	0.659
History of smoking, no. (%)	37 (55.2)	52 (61.2)	0.460
History of drinking, no. (%)	32 (47.8)	36 (42.4)	0.506
Chronic complications, no. (%)			
Hypertension	62 (92.5)	79 (92.9)	0.924
Diabetes mellitus	17 (25.4)	23 (27.1)	0.815
Ischemic heart disease	21 (31.3)	26 (30.6)	0.920
Dyslipidemia	13 (19.4)	19 (22.4)	0.658
Hypothyroidism	6 (9.0)	15 (17.6)	0.123
Asthma or COPD	6 (9.0)	12 (14.1)	0.328
Combined medication, no. (%)			
Loop diuretics	8 (11.9)	11 (12.9)	0.853
Calcium ion antagonist	31 (46.3)	34 (40.0)	0.438
ARB/ACEI	36 (53.7)	42 (49.4)	0.597
β-Receptor antagonist	27 (40.3)	45 (52.9)	0.121
Statin drugs	45 (67.2)	67 (78.8)	0.105
SUA (mg/dL), M ± SD	9.15 ± 1.64	9.13 ± 1.42	0.952
eGFR (mL/min/1.73 m^2), M ± SD	54.60 ± 15.08	54.16 ± 14.85	0.858
CKD stage, no. (%)			0.946
Stage 2 (eGFR of 60–89 mL/min/1.73 m^2)	24 (35.8)	30 (35.3)	
Stage 3 (eGFR of 30–59 mL/min/1.73 m^2)	43 (64.2)	55 (64.7)	
Scr (mg/dL), M ± SD	1.35 ± 0.36	1.40 ± 0.36	0.438
24-h proteinuria (g), M ± SD	0.86 ± 0.68	0.80 ± 0.59	0.576

Comparisons between groups were determined by *t* test or Chi-square test

M mean, *SD* standard deviation, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *ARB/ACEI* angiotensin receptor blocker/angiotensin converting enzyme inhibitors, *SUA* serum uric acid, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *Scr* serum creatinine

compared with allopurinol group (− 2.87 ± 1.48) ($P=0.020$) (Fig. 4b). These data illustrated that febuxostat reduced SUA more effectively compared with allopurinol to some extent in CKD patients complicated with HUA.

Subgroup analysis

All patients were divided into the subgroups of CKD stage 2 and CKD stage 3 according to baseline information (Table 3). For the patients in CKD stage 2, 24-h proteinuria was decreased in febuxostat group compared with allopurinol group at M1 ($P=0.023$) and M3 ($P=0.045$). For the patients in CKD stage 3, eGFR ($P=0.017$) were increased, but SUA ($P=0.002$) were decreased in febuxostat group compared with allopurinol group at M6. Furthermore, eGFR (M6–M0) ($P=0.010$) was increased, while the incidence of eGFR decline ≥ 10% from baseline ($P=0.008$) and SUA change (M6–M0) ($P<0.001$) were decreased in febuxostat group compared with allopurinol group. A more detailed subgroup analysis is displayed in Table 3. This subgroup analysis to a certain degree validated that febuxostat increased eGFR, but decreased SUA more effectively compared with allopurinol in CKD patients with HUA.

Correlation of drug dose with treatment efficiency

All patients were divided into subgroups of febuxostat 40 mg ($n=20$), febuxostat 20 mg ($n=47$), allopurinol 100 mg ($n=56$) and allopurinol 200 mg ($n=29$) according to the dose of each drug (Supplementary Table 1). There was no difference of eGFR, Scr, 24-h proteinuria, SUA among febuxostat 40 mg group, febuxostat 20 mg group, allopurinol 100 mg group or allopurinol 200 mg group at M0, M1, M3 and M6 (all $P>0.05$). And incidence of eGFR decline ≥ 10% from baseline ($P=0.062$), Scr change (M6–M0) ($P=0.153$), 24-h proteinuria

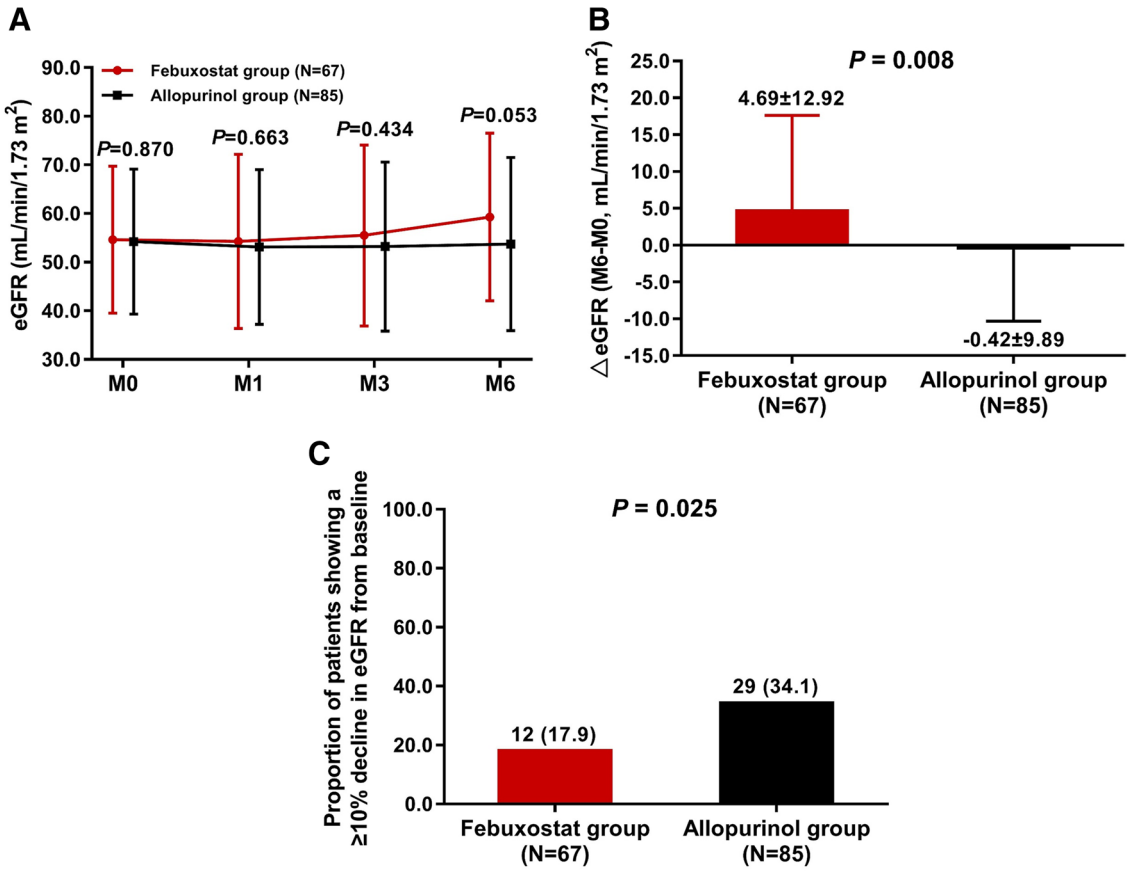

Fig. 2 Comparison of eGFR between febuxostat group and allopurinol group. Comparison of eGFR at different time points (**a**), eGFR change (M6–M0) (**b**) and proportion of patients showing a ≥ 10% decline in eGFR from baseline (**c**) between febuxostat group and allopurinol group in CKD patients complicated with HUA. Comparison between two groups was determined by *t* test or Chi-square test. $P < 0.05$ was considered significant. *CKD* chronic kidney disease, *HUA* hyperuricemia, *eGFR* estimated glomerular filtration rate

change (M6–M0) ($P = 0.307$) and SUA change (M6–M0) ($P = 0.054$) were also similar among these four groups. However, the eGFR change (M6–M0) was different among four groups, and was the highest in febuxostat 40 mg group, followed by febuxostat 20 mg group, and then allopurinol 200 mg group, but decreased in allopurinol 100 mg group ($P = 0.014$). More detailed information of comparison among subgroups is shown in Supplementary Table 1.

Cardiovascular events

There was no cardiovascular mortality in both febuxostat and allopurinol group within 6 months. As for the MACE, there was only one patient with nonfatal myocardial infarction in allopurinol group, while there was no incidence of MACE in febuxostat group during the 6-month treatment ($P = 0.373$).

Discussion

In the present study, we found that in CKD patients complicated with HUA: (1) the proportion of patients showing a ≥ 10% decline in eGFR from baseline was decreased in febuxostat group compared with allopurinol group and febuxostat vs. allopurinol was an independent predictor for reduced risk of eGFR decline ≥ 10% from baseline, which implied that febuxostat effectively attenuated eGFR decline compared with allopurinol in CKD patients complicated with HUA. (2) febuxostat had a stronger potency in reducing Scr and SUA to some extent.

The administration of xanthine oxidase inhibitor ameliorates renal damage via various mechanisms such as inhibition of inflammation and oxidative stress, prevention of glomerular hypertension, etc. [20]. Allopurinol, as a traditional xanthine oxidase inhibitor, is regarded as the most frequently prescribed drug and remains the first-line

Table 2 Univariate and multivariate logistic regression analyses of factors affecting eGFR decline ≥ 10% from baseline

Items	Univariate logistic regression		Multivariate logistic regression	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Febuxostat vs. allopurinol	0.028	0.421 (0.195–0.909)	0.017	0.234 (0.071–0.771)
Age	0.970	1.001 (0.958–1.046)	0.112	0.934 (0.859–1.016)
Gender (male vs. female)	0.664	0.834 (0.368–1.892)	0.162	0.264 (0.041–1.707)
BMI	0.143	0.907 (0.796–1.034)	0.004	0.717 (0.572–0.899)
History of smoking (yes vs. no)	0.709	0.871 (0.422–1.797)	0.324	1.879 (0.536–6.589)
History of drinking (yes vs. no)	0.900	0.955 (0.464–1.964)	0.994	1.005 (0.304–3.319)
Hypertension (yes vs. no)	0.999	–	0.998	–
Diabetes mellitus (yes vs. no)	0.011	2.710 (1.252–5.868)	< 0.001	17.606 (3.842–80.691)
Ischemic heart disease (yes vs. no)	0.191	1.652 (0.779–3.504)	0.368	2.193 (0.397–12.130)
Dyslipidemia (yes vs. no)	0.540	1.305 (0.557–3.059)	0.067	3.597 (0.912–14.185)
Hypothyroidism (yes vs. no)	0.382	0.598 (0.189–1.895)	0.122	0.248 (0.042–1.452)
Asthma or COPD (yes vs. no)	0.082	2.448 (0.892–6.718)	0.009	12.350 (1.880–81.116)
Loop diuretics (yes vs. no)	0.102	0.284 (0.063–1.286)	0.055	0.095 (0.009–1.053)
Calcium ion antagonist (yes vs. no)	0.844	0.930 (0.450–1.921)	0.707	1.264 (0.372–4.293)
ARB/ACEI (yes vs. no)	0.150	1.710 (0.824–3.547)	0.168	2.724 (0.655–11.333)
β-Receptor antagonist (yes vs. no)	0.399	1.362 (0.664–2.794)	0.394	0.512 (0.110–2.385)
Statin drugs (yes vs. no)	0.841	0.920 (0.408–2.074)	0.780	0.814 (0.191–3.470)
SUA	0.043	0.755 (0.575–0.992)	< 0.001	0.314 (0.168–0.590)
eGFR	0.948	0.999 (0.975–1.024)	0.467	0.956 (0.848–1.078)
Scr	0.874	1.084 (0.400–2.937)	0.889	0.675 (0.003–168.312)
24-h proteinuria	0.967	0.988 (0.558–1.751)	0.357	1.784 (0.520–6.121)

"–" indicated that the values could not be calculated due to lack of event

eGFR estimated glomerular filtration rate, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *ARB/ACEI* angiotensin receptor blocker/angiotensin converting enzyme inhibitors, *SUA* serum uric acid, *Scr* serum creatinine

therapy for HUA, while it has some serious adverse effects, such as renal dysfunction, hepatic dysfunction and Stevens–Johnson syndrome [21, 22]. Considering these rare but potentially lethal side effects, its dose needs to be adjusted in the patients with renal dysfunction or renal impairment, leading to insufficient control of HUA, thus alternative therapeutic options are developed in treatment of HUA [23–25]. Febuxostat, as a novel non-purine selective xanthine oxidase inhibitor, has outstanding effect on uric acid-lowering and is well tolerated in long-term treatment in patients with HUA including those are sensitive to allopurinol [26–28]. Some recent clinical studies have been conducted to compare the renal-protective and uric acid-lowering effects between febuxostat and allopurinol in CKD patients [29–31]. For example, one retrospective study compares the renal-protective effect between febuxostat and allopurinol in Korea CKD stage 3 patients complicated with HUA by assessing eGFR change and renal progression-free survival, which reveals that febuxostat retards renal disease progression more effectively than allopurinol [29]. Another retrospective, single-center study compares the effectiveness of allopurinol, febuxostat and benzbromarone on renal function in Taiwanese CKD patients complicated with HUA via evaluating end-stage renal disease incidence, suggesting that patients receiving febuxostat or allopurinol exhibit a comparable risk of renal disease progression and febuxostat is more potent in lowering SUA level compared with allopurinol [31]. In addition, one prospective, single-center cohort study estimates the risk of renal impairment by the change in eGFR during the study in Chinese patients with CKD stage 3–5, which shows that eGFR is increased in febuxostat group but decreased in allopurinol group [30]. These previous studies suggest that febuxostat is non-inferior in reduction of renal impairment compared with allopurinol in CKD patients (high stages) complicated with HUA. However, whether febuxostat still has more benefits on renal protection compared with allopurinol in Chinese patients with lower CKD stage needs further exploration. In the present study, we recruited the CKD (stage 2–3) patients complicated with HUA and assessed the proportion of patients showing a ≥ 10% decline in eGFR from baseline at M6 as the primary outcome according to the definition of previous study, providing further evidence regarding whether febuxostat had a superior renal-protective effect compared with allopurinol [32].

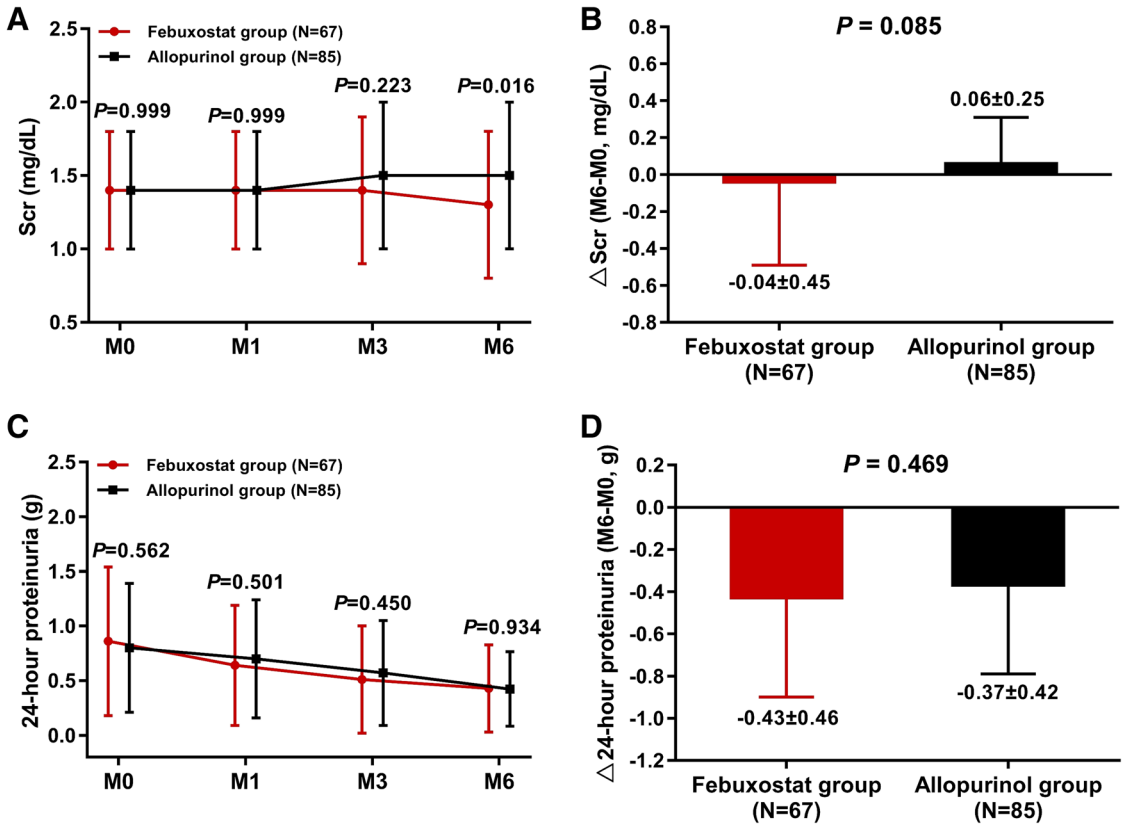

Fig. 3 Comparison of Scr and 24-h proteinuria between febuxostat group and allopurinol group. Comparison of Scr at different time points (**a**), Scr change (M6–M0) (**b**), 24-h proteinuria at different time points (**c**) and 24-h proteinuria change (M6–M0) (**d**) between febuxostat group and allopurinol group in CKD patients complicated with HUA. Comparison between two groups was determined by *t* test. $P < 0.05$ was considered significant. *CKD* chronic kidney disease, *HUA* hyperuricemia, *Scr* serum creatinine

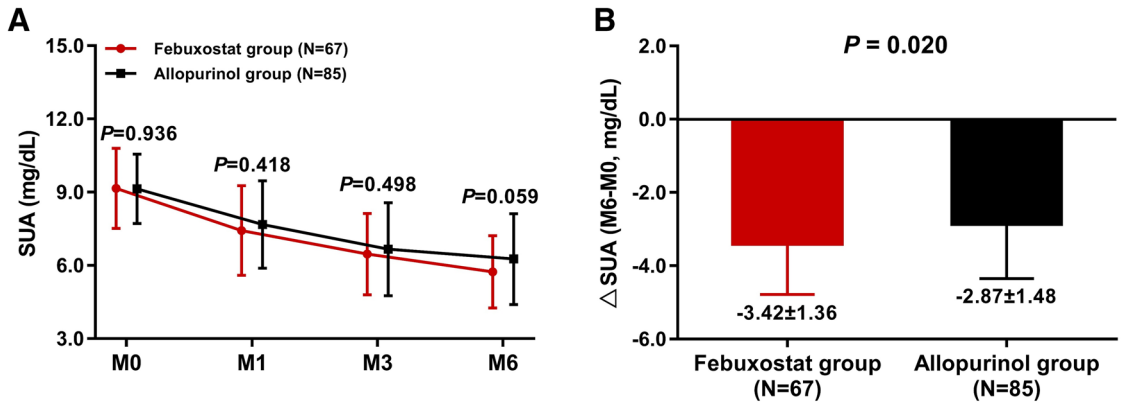

Fig. 4 Comparison of SUA between febuxostat group and allopurinol group. Comparison of SUA at different time points (**a**) and SUA change (M6–M0) (**b**) between febuxostat group and allopurinol group in CKD patients complicated with HUA. Comparison between two groups was determined by *t* test. $P < 0.05$ was considered significant. *CKD* chronic kidney disease, *HUA* hyperuricemia, *SUA* serum uric acid

In our study, we compared the renal-protective effect between febuxostat and allopurinol by assessing eGFR in Chinese CKD (stage 2–3) patients complicated with HUA. And we found that eGFR was numerically higher at M6 and eGFR change (M6–M0) was increased in febuxostat group compared with allopurinol group. Notably, the proportion of patients showing a $\geq 10\%$ decline in eGFR from baseline was decreased in febuxostat group compared with allopurinol

Table 3 Subgroup analysis stratified by CKD stage

Items	CKD stage 2[a] ($n=54$)			CKD stage 3[b] ($n=98$)		
	Febuxostat group ($n=24$)	Allopurinol group ($n=30$)	*P* value	Febuxostat group ($n=43$)	Allopurinol group ($n=55$)	*P* value
M0						
eGFR (mL/min/1.73 m^2), M ± SD	70.87 ± 7.42	71.49 ± 5.71	0.726	45.52 ± 9.58	44.71 ± 8.23	0.653
Scr (mg/dL), M ± SD	1.05 ± 0.15	1.06 ± 0.11	0.847	1.52 ± 0.33	1.58 ± 0.32	0.338
24-h proteinuria (g), M ± SD	0.49 ± 0.38	0.52 ± 0.36	0.744	1.06 ± 0.73	0.95 ± 0.64	0.419
SUA (mg/dL), M ± SD	8.23 ± 1.04	8.33 ± 0.97	0.709	9.66 ± 1.70	9.57 ± 1.43	0.775
M1						
eGFR (mL/min/1.73 m^2), M ± SD	72.95 ± 10.20	70.85 ± 8.63	0.415	43.93 ± 11.62	43.44 ± 9.17	0.815
Scr (mg/dL), M ± SD	1.05 ± 0.13	1.08 ± 0.15	0.472	1.62 ± 0.39	1.65 ± 0.39	0.715
24-h proteinuria (g), M ± SD	0.30 ± 0.20	0.46 ± 0.30	0.023	0.82 ± 0.60	0.83 ± 0.60	0.951
SUA (mg/dL), M ± SD	6.65 ± 2.04	6.48 ± 1.16	0.717	7.87 ± 1.56	8.33 ± 1.74	0.184
M3						
eGFR (mL/min/1.73 m^2), M ± SD	74.93 ± 10.31	70.4 ± 10.91	0.126	44.59 ± 12.16	43.84 ± 12.45	0.767
Scr (mg/dL), M ± SD	1.02 ± 0.12	1.09 ± 0.19	0.143	1.62 ± 0.45	1.69 ± 0.51	0.518
24-h proteinuria (g), M ± SD	0.26 ± 0.18	0.38 ± 0.24	0.045	0.66 ± 0.54	0.68 ± 0.55	0.847
SUA (mg/dL), M ± SD	6.01 ± 1.74	5.32 ± 1.18	0.102	6.72 ± 1.60	7.39 ± 1.82	0.057
M6						
eGFR (mL/min/1.73 m^2), M ± SD	73.93 ± 12.98	70.29 ± 13.57	0.321	51.12 ± 13.43	44.72 ± 12.50	0.017
Scr (mg/dL), M ± SD	1.04 ± 0.14	1.11 ± 0.24	0.275	1.47 ± 0.54	1.65 ± 0.46	0.069
24-h proteinuria (g), M ± SD	0.24 ± 0.22	0.28 ± 0.18	0.560	0.53 ± 0.44	0.50 ± 0.39	0.744
SUA (mg/dL), M ± SD	5.41 ± 1.75	5.04 ± 1.43	0.394	5.90 ± 1.30	6.93 ± 1.74	0.002
ΔeGFR (M6–M0, mL/min/1.73 m^2), M ± SD	3.06 ± 15.02	− 1.21 ± 10.93	0.233	5.60 ± 11.69	0.01 ± 9.36	0.010
eGFR decline ≥ 10% from baseline, no. (%)	6 (25.0)	8 (26.7)	0.890	6 (14.0)	21 (38.2)	0.008
ΔScr (M6–M0, mg/dL), M ± SD	− 0.01 ± 0.21	0.05 ± 0.19	0.306	− 0.05 ± 0.54	0.07 ± 0.27	0.145
Δ24-h proteinuria (M6–M0, g), M ± SD	− 0.25 ± 0.29	− 0.25 ± 0.25	0.981	− 0.53 ± 0.52	− 0.44 ± 0.48	0.407
ΔSUA (M6–M0, mg/dL), M ± SD	− 2.81 ± 1.24	− 3.29 ± 1.48	0.214	− 3.76 ± 1.31	− 2.64 ± 1.45	< 0.001

Comparisons between groups were determined by *t* test or Chi-square test. CKD stage 2[a]: eGFR of 60–89 mL/min/1.73 m^2; CKD stage 3[b]: eGFR of 30–59 mL/min/1.73 m^2

CKD chronic kidney disease, *M* mean, *SD* standard deviation, *SUA* serum uric acid, *eGFR* estimated glomerular filtration rate, *Scr* serum creatinine

group, and multivariate logistic regression analyses further indicated that febuxostat vs. allopurinol was an independent predictor for reduced risk of eGFR decline ≥ 10% from baseline. And data above were supported by subgroup analysis, suggesting that febuxostat had a more effective renal-protective effect compared with allopurinol, which was also consistent with previous studies [29–31]. The possible explanations might include: (1) febuxostat selectively inhibited xanthine oxidase without affecting other activities of purine metabolism, while allopurinol affected the synthesis of hypoxanthine as well as the function of other nucleic acid metabolic enzymes, resulting in some adverse

reactions in kidney and leading to the renal impairment. (2) The metabolite of allopurinol was excreted mainly by kidneys, which might increase renal burden, but febuxostat clearance was predominantly via hepatic metabolism [26]. Hence patients with renal insufficiency were easily at risk of adverse effects caused by allopurinol, and febuxostat might have a stronger renal-protective effect compared with allopurinol. Interestingly, we also observed that asthma or COPD were independent predictors for increased risk of eGFR decline ≥ 10% from baseline. The possible reason might include that (1) patients with asthma or chronic obstructive pulmonary disease (COPD) might need to undergo continuous hormonotherapy (such as glucocorticoid), which might lead to heavy burden to the kidney and even affect renal function in the long term [33]. (2) Additionally, asthma and COPD were a chronic inflammatory disorder of the airways and contributed to chronic hypoxia, and renal tubules were very sensitive to acute injury due to inflammation and oxidative stress [34]. Thus, asthma and COPD were independent predictors for increased risk of eGFR decline. In addition, we also observed that febuxostat reduced SUA and Scr more effectively to a certain degree compared with allopurinol. The possible reason might be that: (1) febuxostat mechanically exerted a greater clinical effect in reducing SUA compared with allopurinol, which was supported by previous studies [29, 30]. (2) The most common dose of febuxostat and allopurinol was 40 mg/day and 300 mg/day, respectively [29]. Considering impaired renal function by allopurinol, dose reduction appeared necessary in patients with renal insufficiency, while dose adjustment of febuxostat was unnecessary due to its great tolerability in all groups of patients. Therefore, in our study, allopurinol dose (200 mg/day) was below the common dose and febuxostat (40 mg/day) was prescribed with the common dose. This might explain the more effective uric acid-lowering ability of febuxostat in our study [26]. Overall, our findings implicated the superior renal-protective effect of febuxostat compared with allopurinol in Chinese CKD (stage 2–3) patients complicated with HUA.

There are still several limitations in our study. (1) Although the sample size of our study was relatively larger compared with majority of previous studies, further study with more samples from more multiple regions throughout China is also needed to validate our results. (2) The observational period of the present study lasted 6 months which was relatively short, thus, further study with longer follow-up period was needed. (3) The detailed mechanism of superior renal-protective effect of febuxostat compared with allopurinol needed to be explored by further animal experiments in the future. (4) As this present study was an observational real-world study, therefore the patients enrolled in our study were not randomized, which might contribute to selection bias and confounding factors in present study. (5) The type of drug allocated was based on the willingness of patients and the clinical status assessed by physical clinicians rather than randomizing patients into febuxostat and allopurinol group, which might lead to selection bias and confounding factors in our study; therefore, further randomized controlled trials studies in the future are needed for validation.

In conclusion, febuxostat presents a superior effect in delaying renal impairment progression compared with allopurinol in CKD patients complicated with HUA.

Compliance with ethical standards

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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